Oath/Declaration

Applicant respectfully states that the post office address for inventor Tani Nishimura is as follows:

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REMARKS

Claims 37-55 are pending. A Versions with Markings to Show Changes Made has been attached for the Examiner's convenience.

Claim Rejections - 35 USC §112, First Paragraph

Claim 50 (and dependent claims 53-55) stand rejected under 35 U.S.C. §112, first paragraph as not being enabled by the specification. Specifically, the Examiner argues that the specification fails to provide enablement for making an anti-plasmodium vaccine. She further alleges that there is a recognition in the art that it is not clear whether a single protein derived from a pathogen is able to elicit protective immunity and cites *Ellis* (p. 571) as authority for this assertion.

Applicant respectfully traverses.

Claim 50 recites an anti-plasmodium vaccine that is comprised of an immunogenic amount of isolated p42 polypeptide and either a QS-21 or ISA51 adjuvant. Applicant's p42 polypeptide is expressed by an insect cell containing a vector which encodes the polypeptide where the polypeptide is comprised of specific fragments of *Plasmodium falciparum* surface protein gp195.

Applicant notes that *Ellis* merely discusses the necessity for the proper identification of the particular protein component of a virus or microbial pathogen effective in eliciting a protective humoral immune response. *Ellis* does not place limits on the size of the protein component or establish what immunological properties the protein component must exhibit as conditions precedent for the production of protective antibodies. Further, any contrary to the

Examiner's suggestion, *Ellis* does not teach of the unpredictability of using a single antigen in a vaccination.

Applicant further argues that the MSP p42 malaria antigen in combination with either QS-21 or ISA51 adjuvant is capable of inducing a protective immune response against *Plasmodium falciparum* infection. In particular, Applicant's experimental data demonstrate that the course and final outcome of *Plasmodium falciparum* infection in malaria-naive *Aotus* monkeys immunized with p42 peptide in combination with QS-21 or ISA51 adjuvant is distinctly different from the course and final outcome of *Plasmodium falciparum* infection in control malaria-naive *Aotus* monkeys, either not immunized or immunized with only adjuvant. In one case, a malaria-naive *Aotus* monkey immunized with p42 in combination with QS21 adjuvant was completely cured from infection (pp. 48, 54-55). The efficacy of MSP p42 malaria antigen in combination with QS-21 or ISA51 adjuvant has thus been unequivocally demonstrated by Applicant's experimental data and test results.

Claim Rejections - 35 USC §103 (*Holder* in view of *Soltysik* and *Saul*)

Claims 37 (and dependent claims 38, 48, and 49) and 50 (and dependent claims 51-55) are rejected under 35 U.S.C. §103(a) as being unpatentable over *Holder et al.* in view of *Soltysik et al.* and *Saul et al.*

Claim 37 recites a pharmaceutical composition for treating plasmodium parasitemia in mammals which is comprised of an isolated p42 polypeptide in combination with either a QS-21 or ISA51 adjuvant.

The Examiner argues that Applicant's invention would be obvious to the ordinarily skilled artisan in light of *Holder* in view of *Soltysik* and *Saul*. The Examiner alleges that *Holder* teaches the sequence of the *Plasmodium falciparum* merozoite major surface antigens (83K, 42K, and 19K), *Soltysik* describes the use of QS-21 as an immunologic adjuvant, and *Saul* teaches the administration of MSP-1 and Montanide ISA720 adjuvant to humans. The Examiner further argues that the *Holder* p42 polypeptide, in view of the *Soltysik* QS-21 immunologic adjuvant, and the *Saul* method of administration, render Applicant's invention unpatentable under 35 U.S.C. §103(a).

The Examiner further states that *Saul* provides the motivation for combining p42 with adjuvant ISA51 because *Saul* teaches that immunogenic compositions containing adjuvants like Montanide ISA720 elicit better immune responses than immunogenic compositions which contain more traditional types of adjuvants.

Applicant respectfully traverses the rejection.

Applicant notes that although *Soltysik* may disclose the use of QS-21 as an immunologic adjuvant in combination with antigens such as ovalbumin and recombinant HIV-1 envelope, the authors in *Saul* acknowledge that "relatively little is known of the minimum critical structure of QS-21 [that is] required for these adjuvant functions" (p. 1403). More particularly, there is no teaching in *Soltysik* which would motivate or compel the ordinarily skilled artisan to select QS-21adjuvant for particular use in combination with MSP p42 malaria antigen, since it is not clear from *Soltysik* how QS-21 functions as an adjuvant in combination with specific antigens. The art of matching an antigen with a suitable adjuvant for the purpose of eliciting a protective immune response in a host organism is unpredictable. There is no fail safe way of assuring that a particular adjuvant will function effectively with a particular antigen in the absence of experimental trial and error. Applicant's experimental data, in particular, demonstrate that some of the adjuvants initially tested with p42 in malaria-naive *Aotus* monkeys (e.g., MF59 and MTP-PE) were not effective and did not alter the course or final outcome of *Plasmodium falciparum* infection in the immunized host animal. In particular, when p42 was combined with either adjuvant MF59 or adjuvant MTP-PE + MF59, the test results were no different from the results obtained for the *Aotus* monkey control group (p. 54). There is, further, no language in *Soltysik* which would motivate or teach the ordinarily skilled artisan to specifically select QS-21 for use with p42, as opposed to other adjuvants which are known in the art. Discovering which adjuvant works optimally in combination with a specific antigen is a "hit or miss" process. There is no predictability in the art for selecting the right adjuvant and no prior art basis exists for determining which adjuvant would be optimal, or even operative, in combination with p42, in the absence of experimental testing.

The experimental data in Applicant's specification indicate that not all of the adjuvants Applicant tested were operative in combination with p42. Applicant's selection of the right adjuvant is clearly the result of inventive effort, since the skilled artisan could not have identified based on the cited prior art an adjuvant specifically or functionally suitable for use with p42. Because the crux of the presently-claimed invention is the specific combination of adjuvant and p42 antigen, a prior art reference which does not teach or suggest the use of either QS-21 or ISA51 adjuvant in specific combination with p42, fails to anticipate the combination of immunologic components claimed by Applicant. The combination of p42 with either QS-21 or ISA51 adjuvant is uniquely engineered to induce protective immunity in response to *Plasmodium falciparum* infection. Any combination which lacks either component of Applicant's combination, would not operate by the same mechanisms, exhibit the same properties, or produce the same effects *in vivo,* as Applicant's invention. Accordingly, the disclosure in *Soltysik* does not teach or motivate the skilled artisan to preferentially select QS-21 from the prior art for use in specific combination with p42 since it does not address *Plasmodium falciparum* generally or p42 specifically.

The Examiner further argues that the administration of an immunogenic composition with a Montanide ISA 720 adjuvant, as disclosed in *Saul,* in view of the previously cited references, is *prima facie* obvious for making and using Applicant's pharmaceutical composition and anti-plasmodium vaccine.

Applicant respectfully traverses.

Applicant notes that *Saul* teaches the use of Montanide ISA 720, instead of the ISA51 adjuvant claimed by Applicant. Montanide 720 is a metabolizable oil-in-water adjuvant which contains a mannide mono-oleate emulsifier (*Lawrence et al.* 1997. Vaccine. 15:176-178). ISA51, in contrast, is a water-in-oil emulsion comparable to Freund's Complete Adjuvant which is made from highly purified raw materials. Although the *Saul* Montanide ISA 720 may be similar to ISA51, it is not identical to Applicant's adjuvant. Further, there are no demonstrations or teachings in *Saul* disclosing how ISA720 would function as an adjuvant in specific combination with p42 to induce a protective immune response against *Plasmodium falciparum* infection. The skilled artisan would thus have no expectation that

the specific combination of Montanide ISA 720 with p42 would be operative against *P. falciparum* infection, and by logical extension, the skilled artisan would have no expectation, based on the *Saul* disclosure and the disclosures of the previously cited references, that the ISA51 and p42 combination would be effective against infection in malaria-naive *Aotus* monkeys, absent experimental testing. Only Applicant's experimental results demonstrate the efficacy of the combination against *Plasmodium falciparum* infection. There is thus no motivation or rational basis in the prior art for the skilled artisan to preferentially select ISA51, instead of other available adjuvants, for use in combination with p42.

Further, the antigen taught in *Saul* is not the equivalent of the merozoite p42 surface protein claimed by Applicant. In contrast to Applicant's antigen, the *Saul* antigen is a merozoite/circumsporozoite protein hybrid that is composed of two conserved blocks of merozoite surface protein-1 fused to a circumsporozoite protein T cell epitope. Applicant's p42 polypeptide does not contain amino acid residues from the sporozoite coat protein. Each component of the antigen/adjuvant combination disclosed in *Saul* is therefore distinct and different from each component of the antigen/adjuvant combination claimed by Applicant. The fact that the *Saul* combination might be administerable to humans is irrelevant since the combination taught in *Saul* does not encompass, suggest, or provide motivation for putting together the immunologic combination that is taught by Applicant. There is no demonstration in *Soltysik* that QS-21 adjuvant is appropriate for use in specific combination with p42 for inducing a protective immune response against *Plasmodium falciparum* in malaria-naive *Aotus* monkeys.

In sum, the *Soltysik* QS-21 adjuvant in combination with a non-p42 antigen, in view of the *Saul* method of administering a sporozoite/merozoite hybrid antigen with a non-Montanide ISA51 adjuvant is not *prima facie* evidence under 35 U.S.C. §103 for making and using Applicant's pharmaceutical composition or anti-plasmodium vaccine. The *Holder* reference, further, does not teach the immunologic combination claimed by Applicant, and in combination with *Soltysik* and *Saul* does not, either singly or in combination, suggest adjuvants which are specifically operable in combination with p42.

Obvious to Try is NOT the Standard for Patentability

As indicated above, the Examiner's assertion that it would have been *prima facie* obvious, based on the prior art, for the skilled artisan to use QS-21 or ISA51 adjuvant in combination with p42 is erroneous. The skilled artisan would not have been able to pick out QS-21 or ISA51 adjuvant from the prior art for use in specific combination with p42. *Soltysik* says nothing about the suitability of QS-21 in combination with p42 for eliciting a protective antibody response. *Saul* does nothing to overcome the uncertainty in the art regarding the appropriate selection of adjuvant for specific use in combination with a particular antigen. Examiner's arguments appear to presume that the suitability of a particular adjuvant for use in specific combination with p42 would be known prior to experimental testing.

To the extent the Examiner is asserting that it would have been obvious to try using QS-21 or ISA51 adjuvant in combination with p42, based on the prior art, the Court of Appeals for the Federal Circuit has repeatedly held that "obvious to try" and "obvious to experiment" are not the appropriate standards for determining the obviousness of a claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir.1986); *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir.1988).

> An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the desired result would be obtained if certain directions were followed.

In re Eli Lilly & Co., 14 USPQ2d 1741 (Fed. Cir.1990) stands for the proposition that it is improper for the Examiner to assert that it would have been obvious to explore a new technology, or a general approach that seems to be a promising field of experimentation, based on a generic and largely irrelevant reference.

To the extent the Examiner is asserting that it would have been obvious to try using either QS-21 or ISA51 adjuvant in combination with p42 for eliciting a protective immune response, the argument is improper and does not support the Examiner's obvious rejection

based on the cited references. Applicant respectfully submits that the claimed invention is patentably distinct from the prior art in that it was not obvious to combine the QS-21 or ISA51 adjuvant and p42 immunological elements of Applicant's claimed composition in light of the prior art, particularly in view of the lack of any teaching or motivation in the references to create Applicant's specific immunological combination against *Plasmodium falciparum*.

Accordingly, Applicant respectfully requests withdrawal of the Examiner's rejection under 35 U.S.C. §103 of Claim 37 (and dependent claims 38, 48, and 49) and Claim 50 (and dependent claims 51-55), since the cited references fail to disclose or suggest Applicant's pharmaceutical composition and/or anti-plasmodium vaccine.

Claim Rejections - 35 USC §103 (*Holder* in view of *Murphy* and *Smith*)

Claim 37 (and dependent claims 39-47) is rejected under 35 U.S.C. §103(a) as being unpatentable over *Holder et al.* in view of *Murphy et al.* and *Smith et al.* The Examiner argues that the *Smith* teaching of a recombinant baculovirus expression vector capable of expressing a selected gene in a host insect cell, and the *Murphy* teaching of a recombinantly produced p42 from the WEL *Plasmodium falciparum* strain (also in a host insect cell), render Applicant's pharmaceutical composition *prima facie* obvious under 35 U.S.C. §103.

Applicant respectfully traverses the rejection.

Initially, Applicant notes that Claim 50, rather than Claim 37, recites "the expression of a p42 polypeptide by an insect cell which contains a vector encoding the polypeptide."

Applicant further notes that the crux of the presently-claimed invention is the QS-21 or ISA51 adjuvant in specific combination with an MSP p42 malaria antigen. In particular, each one of Applicant's claims requires either QS-21 or ISA51 adjuvant in specific combination with p42. Since none of *Holder*, *Smith* or *Murphy* teach or suggest this aspect of the claimed invention, and without a more pertinent prior art reference than the *Soltysik* and *Saul* disclosures distinguished above, the Examiner has failed to make a *prima facie* case of obviousness. For these reasons, the Examiner's rejection under 35 U.S.C. §103 of Claim 37 (and claims 39-47 which depend therefrom), should be withdrawn.

Based upon the foregoing, it is submitted that Claims 37-55 are patentable over the art of record.

The Commissioner is authorized to charge any additional fees including extension fees or other relief which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-67984-/RFT/TAL/NBC).

CONCLUSION

Applicants respectfully submit that the Claims are now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

FLEHR HOHBACH TEST
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Date: December 17, 2001

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VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning at page 1, line 2, has been amended as follows:

– This application is a continuation-in-part of Application No.:08/195,705, filed February 15, 1994, now Patent No. _____. This invention was made with Government support under Contract DPE0453A00901500 of the Agency for International Development. The Government has certain rights in this invention.—